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(71)Applicant : MIKASA SEIYAKU KK
(72)Inventor : OMURA HISAKO
WADA YOSHIO
YAMADA YOSHIHARU
MIZUNO KEIZO

(54) EXTERNAL PREPARATION CONTAINING PRIDINOL MESILATE

(57)Abstract:
PURPOSE: To obtain a pridinol mesilate-containing external preparation excellent in percutaneous absorbability and useful as a skeletal muscle relaxant.
CONSTITUTION: Pridinol mesilate is compounded with glycerol and benzylalcohol preferably in amounts of 1-50wt.% and 1-20wt.%, respectively. The external preparation is preferably formed into a plaster. The simultaneous use of the benzylalcohol and the glycerol as percutaneous absorption-promoting agents gives such the high percutaneous absorption of the pridinol mesilate as being not given by the simultaneous use of propylene glycol or 1,3-butylene glycol. When the glycerol is compounded in a large amount, the percutaneous absorption of the pridinol mesilate is lowered, while when compounded in a small amount, the dispersibility of the pridinol mesilate is deteriorated on the formation of the medicinal preparation to lower workability and uniformity. The external preparation is excellent in percutaneous absorbability, maintains an effective concentration in blood for a long time, can easily be used, and is little in side effects.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] this invention relates to the mesyl acid PURIJI Norian content medicine for external application excellent in the percutaneous absorption containing mesyl acid PURIJI Norian useful as a skeletal muscle relaxant.
[0002]
Background of the Invention] As a medication method aiming at systemic action, the case where it is generally based on internal use or injection is almost the case. By medication by injection, medication with the short frequent medicine of biological half-life is needed by not avoiding the metabolism (the first time passage effect) in liver in internal use, and maintenance of medicine blood drug concentration is difficult. Then, the treatment system prescribed for the patient by carrying out osmosis absorption of the medicine from the skin attracts attention as a new medication method. In the case of dermal administration, a previous fault is conquered and mitigation of the number of times of medication, improvement in compliance, and discontinuation of medication have which easy advantage.
[0003] Mesyl acid PURIJI Norians are the center nature which has the chemical name of 1 and 1-Diphenyl-3-piperidinopropanol methanesulfonate (molecular formula :C20H25NO-CH3SO3 H), especially physic matter commonly used as a line hypersthenia remission agent which has principal action in the interneurone in the spinal cord. Although many mesyl acid PURIJI Norians are usually used as an internal use agent and injection, medication of a ter in die is usually needed and, as for the internal use agent, side effects, such as digestive trouble, such as anorexia, heartburn, and stomach stomach reclining, epigastric distress, etc., and a liver, a renal-function obstacle, pose a problem. On the other hand, in the injection, it has the fault of being easy to discover side effects, such as wandering by rapid elevation of blood drug concentration, with the sharp pain at the time of medication.
[0004] Then, although the skeletal muscle relaxation percutaneous absorption agent (refer to JP,6-336434,A) which made the water-soluble polymer contain mesyl acid PURIJI Norian is proposed recently, the effective blood drug concentration expected by this percutaneous absorption agent cannot fully be maintained, and elevation of the blood drug concentration beyond this cannot be expected. Moreover, since mesyl acid PURIJI Norian more than saturated concentration contains, the crystal deposit of mesyl acid PURIJI Norian takes place, adhesiveness falls in connection with this, and it has the trouble that a feeling of use also becomes bad. Therefore, it excels in percutaneous absorption, and effective blood drug concentration is maintained for a long time, and use is simple, and development of a mesyl acid PURIJI Norian content medicine for external application with few side effects is desired.
[0005]
[Description of the Invention] This invention persons succeeded in development of the mesyl acid PURIJI Norian content medicine for external application which was excellent in percutaneous absorption and durability, and was excellent in a feeling of use by making a glycerol and benzyl alcohol blend with mesyl acid PURIJI Norian, as a result of repeating research wholeheartedly in such a situation. That is, this invention offers the mesyl acid PURIJI Norian content medicine for external application characterized by the bird clapper from mesyl acid PURIJI Norian, a glycerol, benzyl alcohol, and an external application basis, and this invention offers further the mesyl acid PURIJI Norian content medicine for external application which is the thing of a pasting agent as a thing of the desirable pharmaceutical form of this medicine for external application.
[0006] Hereafter, this invention is explained in detail. Generally glycols, such as glycerol, propylene-glycol, ethylene glycol, 1, and 3-butylene glycol, are blended with the medicine for external application for the purpose of broad uses, such as a stabilizing agent, a plasticizer, a solubilizing agent, a wetting agent, a softener, a binder, an excipient, a dispersant, a desiccant, a preservative, a solvent, and a resolvent, and it is an important component in tablet development. Let especially glycols be indispensable components in the pasting agent. In these glycols, propylene-glycol and 1, and 3-butylene glycol The operation which will reinforce a percutaneous absorption facilitatory effect further if the percutaneous absorption facilitatory effect of a medicine is in itself besides the above-mentioned combination purpose and it combines with other penetration enhancers, Namely, although having a combined effect is reported (B. refer to W.Barry, Journal of Controlled Release, and 6 (1987) 85-97 grade), even if it is glycols of the same kind It is thought that a glycerol cannot expect a percutaneous absorption facilitatory effect and a combined effect, and a report that such [actually] an effect was acquired is not found.
[0007] this invention finds out that the percutaneous absorption promotion nature of mesyl acid PURIJI Norian does a high absorption promotion operation so exceeding anticipation when a combined effect uses together the glycerol considered to be a low, in spite of not accepting exceptionally in the combined use with the propylene glycol generally said for a combined

effect with a penetration enhancer to be high, or 1 and 3-butylene glycol. That is, this invention finds out that the high percutaneous absorption of mesyl acid PURIJI Norian which is not obtained is acquired by the combined use with a propylene glycol or 1 and 3-butylene glycol by using together the benzyl alcohol and the glycerol which are a penetration enhancer.
[0008] The blending ratio of coal of the glycerol in the medicine for external application concerning this invention is preferably blended at 10 - 25% still more preferably 5 to 30% one to 50% of the weight (in this specification, it only displays by % hereafter). If there are many loadings of a glycerol, the inclination for the percutaneous absorption of mesyl acid PURIJI Norian to fall will be seen. On the other hand, if there are few loadings, the problem that the dispersibility of a fine-particles component is bad and lacks in workability and homogeneity on the occasion of tablet-izing will arise. Moreover, since plasticity becomes [a pharmaceutical form] bad about the thing of a pasting agent, the good pasting agent of a feeling of use is not obtained. Moreover, a glycerol is matter which has the advantage that it is low stimulative as compared with other glycols.
[0009] On the other hand, the blending ratio of coal of benzyl alcohol is preferably blended at 5 - 10% still more preferably 1 to 20% 0.1 to 50%. if the loadings of benzyl alcohol increase -- own phase separation of benzyl alcohol -- it looms and becomes easy to produce ** Moreover, it becomes [if there are few loadings, the homogeneity of mesyl acid PURIJI Norian will become bad, and] the cause of making percutaneous absorption falling and is not desirable. Moreover, benzyl alcohol acts as a solubilizing agent, in a tablet, it dissolves, mesyl acid PURIJI Norian is distributed uniformly, and it is thought that the operation which suppresses the deposit of a crystal is made.
[0010] A eucalyptus oil, a monochrome caprylic-acid propylene glycol, a peppermint oil, an adipic-acid diisopropyl, lauryl alcohol, a myristic-acid isopropyl, oleic acid, etc. can also be blended with the medicine for external application concerning this invention as other absorption accelerators currently generally used. Although the percutaneous absorption of mesyl acid PURIJI Norian is so good that pH is high, as for pH of a tablet, it is desirable to prepare by pH five to 8 within the limits in consideration of the percutaneous absorption of mesyl acid PURIJI Norian and the advantage of tablet-izing.
[0011] Generally the medicine for external application concerning this invention can be tablet-ized to the thing of a pharmaceutical form well-known as an external application tablet. As a pharmaceutical form of this tablet, a pasting agent, a patch agent, a tape, ointment, gel, cream pharmaceuticals, solution, etc. are mentioned.
[0012] Especially as an external application basis added by the medicine for external application concerning this invention, it is not restricted but the water soluble polymer usually used, a surfactant, a stabilizing agent, pH regulator, etc. can be mentioned. As a water soluble polymer, all of a polyacrylic acid, sodium polyacrylate, a carboxyvinyl polymer, KARUME sirloin sodium, polyvinyl alcohol, a polyvinyl pyrrolidone, hydroxypropylcellulose, a hydroxyethyl cellulose, an ethyl cellulose, an alginic acid, a sodium alginate, gelatin, and a methyl vinyl ether, a maleic-anhydride copolymer, etc. are usable, for example.
[0013] As a surfactant, polyoxyethylene sorbitan fatty acid ester, a sorbitan fatty acid ester, polyoxyethylene alkyl phenyl ether, etc. can be mentioned, for example. As a stabilizing agent, a sodium hydrogensulfite, L ascorbic acid, a sodium ascorbate, burylhydroxyanisole, butylhydroxytoluene, a propyl gallate, tocopherol acetate, an dl-alpha-tocopherol, a sodium hydrogensulfite, etc. are mentioned, for example.
[0014] As a pH regulator, a diisopropanolamine, a diethanolamine, a triethanolamine, a citric acid, a tartaric acid, etc. are mentioned, for example. As a pharmaceutical form of the medicine for external application concerning this invention, since the absorptivity (durability) of a medicine, safety, and use are simple, a pasting agent is the most desirable pharmaceutical form. A cross linking agent, a bulking agent, etc. which are usually used besides each above-mentioned basis are suitably used for this pasting agent.
[0015] As a cross linking agent, aluminium compounds, such as inorganic or the salt of an organic acid like an aluminum hydroxide and an aluminum stearate, double salt like aluminum alum, inorganic nature aluminum complex salt, and an organic nature aluminum chelate compound, are mentioned, for example. Moreover, as a bulking agent, a kaolin, titanium oxide, a zinc oxide, a silicic acid anhydride, etc. are mentioned, for example. In addition to this, a thickener, a tackifier, antiseptics, an aromatizing agent, a coloring agent, etc. can be suitably blended with the medicine for external application of this invention if needed.
[0016] Although an example explains this invention concretely below, this invention is not limited to the following example, unless the main point is changed.
[0017] An example 1 and an example 2 (pasting agent)

処方	実施例1	実施例2
(1) 水溶性高分子	8.0	8.0
(2) 架橋剤	0.81	0.81
(3) 充填剤	0.25	0.25
(4) ﾒﾁﾙﾊﾟﾗﾍﾞﾝ	0.1	0.1
(5) ﾌﾟﾛﾋﾟﾙﾊﾟﾗﾍﾞﾝ	0.05	0.05
(6) ｸﾞﾘｾﾘﾝ	25.0	25.0
(7) ﾍﾞﾝｼﾞﾙｱﾙｺｰﾙ	5.0	5.0
(8) 界面活性剤	1.0	1.0
(9) ﾒｼﾙ酸ﾌﾞﾘｼﾞﾉｰﾙ	0.5	1.0
(10) ｴﾃﾞﾄ酸ﾅﾄﾘｳﾑ	0.25	0.25
(11) pH調整剤	0.6	0.6
(12) 精製水	57.94	57.44
合　計	100.0%	100.0%

[Table 1] Table 1

[0018] (A) (1) An agitator may be used and - (6) is mixed, and (7) which melted (8) further is added and it often mixes.
(B) (9) - (11) is dissolved in (12).
(C) Add (B) to (A) and carry out churning mixture uniformly.
(D) Spread this plaster body to a nonwoven fabric, cover with polyester film, and obtain a pasting agent.
[0019] Example 3 (gel)

(処方)

(1) メシル酸ブリジノール	1%
(2) グリセリン	10%
(3) ベンジルアルコール	5%
(4) 水溶性高分子	2%
(5) pH調整剤	適量
(6) 精製水	適量
合計	100%

(A) Make (6) swell (4).
(B) Dissolve (1) in (2) and (3).
(C) Agitate until it adds (A) and (5) to (B) and the whole becomes uniform, and consider as gel.
[0020] Example 4 (liquid medicine)

(処方)

(1)メシル酸ブリジノール	1%
(2)ベンジルアルコール	5%
(3)グリセリン	20%
(4)pH調整剤	適量
(5)精製水	適量
合計	100%

(A) (1) Dissolution mixture of - (5) is carried out uniformly, and it considers as liquid medicine.
[0021] The example 1 of comparison, and the example 2 (pasting agent) of comparison

処　方	比較例1	比較例2
(1) 精製水	55.95	55.45
(2) 酒石酸	0.9	0.9
(3) ﾒｼﾙ酸ﾌﾞﾘｼﾞﾉｰﾙ	0.5	1
(4) ｸﾞﾘｾﾘﾝ	30	30
(5) 軽質無水ｹｲ酸	2	2
(6) 水溶性高分子	7	7
(7) 架橋剤	0.2	0.2
(8) 界面活性剤	0.6	0.6
(9) ﾊｯｶ油	1	1
(10) ｼﾞｲｿﾌﾟﾛﾊﾟﾉｰﾙｱﾐﾝ	適量	適量
合　計	100.0%	100.0%

[Table 2] Table 2

[0022] (A) Add (2) and (3) to (1) and dissolve in it.
(B) Add (4) - (10) to (A) and mix with it uniformly.
(C) Spread this plaster body to a nonwoven fabric, cover with polyester film, and obtain a pasting agent.
[0023] The example 3 (gel) of comparison

(処方)

(1)	メシル酸プリジノール	1%
(2)	ベンジルアルコール	5%
(3)	水溶性高分子	2%
(4)	pH調整剤	適量
(5)	精製水	適量
	合計	100%

(A) Make (5) swell (3).
(B) Dissolve (1) in (2).
(C) Agitate until it adds (A) and (4) to (B) and the whole becomes uniform, and consider as gel.
[0024] The example 4 (gel) of comparison

(処方)

(1)	メシル酸プリジノール	1%
(2)	グリセリン	10%
(3)	水溶性高分子	2%
(4)	pH調整剤	適量
(5)	精製水	適量
	合計	100%

(A) Make (5) swell (3).
(B) Dissolve (1) in (2).
(C) Agitate until it adds (A) and (4) to (B) and the whole becomes uniform.
[0025] The example 5 (liquid medicine) of comparison

(処方)

(1)	メシル酸プリジノール	1%
(2)	ベンジルアルコール	5%
(3)	プロピレングリコール	20%
(4)	pH調整剤	適量
(5)	精製水	適量
	合計	100%

(A) (1) Dissolution mixture of - (5) is carried out uniformly.
[0026] The example 6 (liquid medicine) of comparison

(処方)

(1)	メシル酸プリジノール	1%
(2)	ベンジルアルコール	5%
(3)	1，3－ブチレングリコール	20%
(4)	pH調整剤	適量
(5)	精製水	適量
	合計	100%

(A) (1) Dissolution mixture of - (5) is carried out uniformly.
[0027] The example [of an examination] 1 experiment method: The pasting agent prepared by the method indicated for the example 2, the example 1 of comparison, and the example 2 of comparison was sealed with the aluminum lamination wrapping material, and after saving for two weeks in a 60-degree C thermostat, the appearance change on the front face of a plaster body was observed. The result is shown in Table 3.
Result: Although the deposit of the crystal of mesyl acid PURIJI Norian was accepted in all about the pasting agent of the example 1 of comparison, and the example 2 of comparison, in the pasting agent of the example 2 in this invention, the deposit of a crystal was not seen at all.
[0028]

[Table 3] Table 3

処 方	外 観
実施例2	変化なし
比較例1	メシル酸プリジノールの結晶が析出
比較例2	メシル酸プリジノールの結晶が析出

[0029] The comparison examination of skin permeability was carried out to example of examination 2 example 1, the example 2, the example 1 of comparison, and the example 2 of comparison by the following experiment method about each pasting agent prepared by the method of a publication. The result is shown in drawing 1 .
The experiment method: It carried out depilating of the regions-of-back hair of 7 weeks old and a femaleness hair loess rat (135g of average weight) by electric hair clipper on the experiment previous day. After carrying out cervical-vertebra luxation of the hair loess rat which carried out depilating on the previous day, the regions-of-back skin was extracted. The extraction skin was fixed to the Francis type diffusion cell (diameter of 2cm), the pasting agent (they are about 1.3mg (an example 1,

example 1 of comparison) and about 2.7mg (an example 2, example 2 of comparison) as mesyl acid PURIJI Norian) of examples 1 and 2 and the examples 1 and 2 of comparison was stuck on the donor side, respectively, and the physiological saline was filled to the receptor side. During the experiment, the receptor side maintained 37 degrees C and agitated them with the magnetic stirrer. The constant rate was extracted from the receptor side for every predetermined time, and the amount of transparency of mesyl acid PURIJI Norian was measured using the high performance chromatography.
[0030] Result: As compared with the thing of each example of comparison, penetrable elevation was seen with elevation of medicine concentration, and, as for this invention article, high percutaneous absorption was accepted so that clearly from drawing 1 . Since it compared with this and saturated concentration was already reached with 0.5% (example 1 of comparison) of medicine concentration in the example of comparison, the penetrable elevation beyond this was not seen as for 1.0% (example 2 of comparison) of medicine concentration, but percutaneous absorption was low as compared with this invention article.
[0031] The absorption moving state was measured about each pasting agent prepared by the method of a publication for the example of examination 3. example 2, and the example 2 of comparison.
The experiment method: It carried out depilating of the regions-of-back hair of 8 weeks old and a femaleness hair loess rat (136.5g of average weight) by electric hair clipper on the experiment previous day, and abstained from food further. the pasting agent (4x2.5cm) of an example 2 and the example 2 of comparison -- the median line was avoided on the rat regions-of-back skin which carried out depilating of the one sheet (about 7mg as mesyl acid PURIJI Norian) on the previous day, it stuck on right-hand side, and a it top was fixed by the adhesive tape for fixation, and the surge cull tape (3M) was stuck and it fixed so that the truncus section might be wrapped in further It collected blood in 4ml of blood from the abdomen inferior vena cava under anesthesia after (medication 4 and 8 and 16 hours). After having taken 0.75ml of blood serums after centrifugal separation (3000rpm, 20 minutes), making blood alkaline by the sodium hydroxide and extracting mesyl acid PURIJI Norian using the petroleum ether, the concentration in a blood serum was measured using the high performance chromatography.
[0032] Result: Each measured value which shows the pharmacokinetics is shown in Table 4. The pasting agent of this invention maintained the mesyl acid PURIJI Norian concentration in blood stabilized until after 16 hours, and Cmax and AUC have exceeded it under the influence of an absorption accelerator as compared with the example 2 of comparison, and high percutaneous absorption was accepted.
[0033]

[Table 4] Table 4

製剤	投与量	血中濃度 (ng/ml) 4hr	8hr	16hr	Tmax (hr)	Cmax (ng/ml)	AUC (ng·hr/ml)
実施例2	7mg/ラット	89.4	110.2	80.1	8	110.2	1258.8
比較例2	7mg/ラット	56.8	84.9	51.4	8	84.9	742.9

(Note) Tmax : The highest blood-drug-concentration attainment time Cmax : The highest blood drug concentration AUC : Blood-drug-concentration time curvilinear inferior-surface-of-tongue product [0034] The comparison examination of skin permeability was carried out to the example 2 of an examination by the method of a publication about each gel prepared by the method indicated for the example of examination 4. example 3, the example 3 of comparison, and the example 4 of comparison. Moreover, observation of appearance and comparison of a feeling of inunction were performed simultaneously. The result of a skin permeability examination is shown in drawing 2 .
Result: Although it is inferior to percutaneous absorption and the facilitatory effect was seen [the glycerol of the example 4 of comparison] also by the benzyl alcohol independent of the example 3 of comparison so that clearly from drawing 2 , it was admitted that this invention article blended combining both maintained high percutaneous absorption. moreover, the thing for which this invention article (example 3) blends a glycerol although benzyl alcohol looms in the example 3 of comparison, ** is seen observation of appearance, and as a result of comparison of a feeling of an application and a feeling of inunction is bad -- the dispersibility of benzyl alcohol -- good -- becoming -- moreover, benzyl alcohol -- also coming up -- it did not accept but the improvement of a feeling of inunction was accepted
[0035] The comparison examination of skin permeability was carried out to the example of examination 5. example 4, the example 5 of comparison, and the example 6 of comparison by the method of a publication about each solution prepared by the method of a publication at the example 2 of an examination. The result is shown in drawing 3 .
Result: As compared with the solution by combination with the propylene glycol which was shown in the example of comparison and which is said for there to be a percutaneous absorption promotion operation generally, or 1 and 3-butylene glycol, very high percutaneous absorption was accepted in the solution blended combining the benzyl alcohol and the glycerol of this invention article so that clearly from drawing 3 .

[Translation done.]

CLAIMS

[Claim(s)]
[Claim 1] The mesyl acid PURIJI Norian content medicine for external application characterized by the bird clapper from mesyl acid PURIJI Norian, a glycerol, benzyl alcohol, and an external application basis.
[Claim 2] The medicine for external application according to claim 1 whose benzyl alcohol the above-mentioned glycerol is 5 - 30 % of the weight, and is 1 - 20 % of the weight.
[Claim 3] The medicine for external application according to claim 1 or 2 whose pharmaceutical form of the above-mentioned medicine for external application is the thing of a pasting agent.

[Translation done.]

TECHNICAL FIELD

[Industrial Application] this invention relates to the mesyl acid PURIJI Norian content medicine for external application excellent in the percutaneous absorption containing mesyl acid PURIJI Norian useful as a skeletal muscle relaxant.

[Translation done.]

PRIOR ART

Background of the Invention] As a medicine prescribing [for the patient]-a medicine method aiming at systemic action, the case where it is generally based on internal use or injection is almost the case. By internal use, it is the metabolism in liver.

[Translation done.]

EFFECT OF THE INVENTION

By medication by injection, medication with the short frequent medicine of biological half-life is needed by not avoiding the (first time passage effect), and maintenance of medicine blood drug concentration is difficult. Then, the treatment system prescribed for the patient by carrying out osmosis absorption of the medicine from the skin attracts attention as a new medication method. In the case of dermal administration, a previous fault is conquered and mitigation of the number of times of medication, improvement in compliance, and discontinuation of medication have which easy advantage.
[0003] Mesyl acid PURIJI Norians are the center nature which has the chemical name of 1 and 1-Diphenyl-3-piperidinopropanol methanesulfonate (molecular formula :C20H25NO-CH3SO3 H), especially physic matter commonly used as a line hypersthenia remission agent which has principal action in the interneurone in the spinal cord. Although many mesyl acid PURIJI Norians are usually used as an internal use agent and injection, medication of a ter in die is usually needed and, as for the internal use agent, side effects, such as digestive trouble, such as anorexia, heartburn, and stomach stomach reclining, epigastric distress, etc., and a liver, a renal-function obstacle, pose a problem. On the other hand, in the injection, it has the fault of being easy to discover side effects, such as wandering by rapid elevation of blood drug concentration, with the sharp pain at the time of medication.
[0004] Then, although the skeletal muscle relaxation percutaneous absorption agent (refer to JP,6-336434,A) which made the water-soluble polymer contain mesyl acid PURIJI Norian is proposed recently, the effective blood drug concentration expected by this percutaneous absorption agent cannot fully be maintained, and elevation of the blood drug concentration beyond this cannot be expected. Moreover, since mesyl acid PURIJI Norian more than saturated concentration contains, the crystal deposit of mesyl acid PURIJI Norian takes place, adhesiveness falls in connection with this, and it has the trouble that a feeling of use also becomes bad. Therefore, it excels in percutaneous absorption, and effective blood drug concentration is maintained for a long time, and use is simple, and development of a mesyl acid PURIJI Norian content medicine for external application with few side effects is desired.
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[Description of the Invention] This invention persons succeeded in development of the mesyl acid PURIJI Norian content medicine for external application which was excellent in percutaneous absorption and durability, and was excellent in a feeling of use by making a glycerol and benzyl alcohol blend with mesyl acid PURIJI Norian, as a result of repeating research wholeheartedly in such a situation. That is, this invention offers the mesyl acid PURIJI Norian content medicine for external application characterized by the bird clapper from mesyl acid PURIJI Norian, a glycerol, benzyl alcohol, and an external application basis, and this invention offers further the mesyl acid PURIJI Norian content medicine for external application which is the thing of a pasting agent as a thing of the desirable pharmaceutical form of this medicine for external application.
[0006] Hereafter, this invention is explained in detail. Generally glycols, such as glycerol, propylene-glycol, ethylene glycol, 1, and 3-butylene glycol, are blended with the medicine for external application for the purpose of broad uses, such as a stabilizing agent, a plasticizer, a solubilizing agent, a wetting agent, a softener, a binder, an excipient, a dispersant, a desiccant, a preservative, a solvent, and a resolvent, and it is an important component in tablet development. Let especially glycols be indispensable components in the pasting agent. In these glycols, propylene-glycol and 1, and 3-butylene glycol The operation which will reinforce a percutaneous absorption facilitatory effect further if the percutaneous absorption facilitatory effect of a medicine is in itself besides the above-mentioned combination purpose and it combines with other penetration enhancers, Namely, although having a combined effect is reported (B. refer to W.Barry, Journal of Controlled Release, and 6 (1987) 85-97 grade), even if it is glycols of the same kind It is thought that a glycerol cannot expect a percutaneous absorption facilitatory effect and a combined effect, and a report that such [actually] an effect was acquired is not found.
[0007] this invention finds out that the percutaneous absorption promotion nature of mesyl acid PURIJI Norian does a high absorption promotion operation so exceeding anticipation by using together the glycerol considered that a combined effect is low in spite of not accepting exceptionally in the combined use with the propylene glycol generally said for a combined effect with a penetration enhancer to be high, or 1 and 3-butylene glycol. That is, this invention finds out that the high percutaneous absorption of mesyl acid PURIJI Norian which is not obtained is acquired by the combined use with a propylene glycol or 1 and 3-butylene glycol by using together the benzyl alcohol and the glycerol which are a penetration enhancer.
[0008] The blending ratio of coal of the glycerol in the medicine for external application concerning this invention is preferably blended at 10 - 25% still more preferably 5 to 30% one to 50% of the weight (in this specification, it only displays by % hereafter). If there are many loadings of a glycerol, the inclination for the percutaneous absorption of mesyl acid PURIJI Norian to fall will be seen. On the other hand, if there are few loadings, the problem that the dispersibility of a fine-particles

component is bad and lacks in workability and homogeneity on the occasion of tablet-izing will arise. Moreover, since plasticity becomes [a pharmaceutical form] bad about the thing of a pasting agent, the good pasting agent of a feeling of use is not obtained. Moreover, a glycerol is matter which has the advantage that it is low stimulative as compared with other glycols.

[0009] On the other hand, the blending ratio of coal of benzyl alcohol is preferably blended at 5 - 10% still more preferably 1 to 20% 0.1 to 50%. if the loadings of benzyl alcohol increase -- own phase separation of benzyl alcohol -- it looms and becomes easy to produce ** Moreover, it becomes [if there are few loadings, the homogeneity of mesyl acid PURIJI Norian will become bad, and] the cause of making percutaneous absorption falling and is not desirable. Moreover, benzyl alcohol acts as a solubilizing agent, in a tablet, it dissolves, mesyl acid PURIJI Norian is distributed uniformly, and it is thought that the operation which suppresses the deposit of a crystal is made.

[0010] A eucalyptus oil, a monochrome caprylic-acid propylene glycol, the peppermint oil, an adipic-acid diisopropyl, lauryl alcohol, a myristic-acid isopropyl, oleic acid, etc. can also be blended with the medicine for external application concerning this invention as other absorption accelerators currently generally used. Although the percutaneous absorption of mesyl acid PURIJI Norian is so good that pH is high, as for pH of a tablet, it is desirable to prepare by pH five to 8 within the limits in consideration of the percutaneous absorption of mesyl acid PURIJI Norian and the advantage of tablet-izing.

[0011] Generally the medicine for external application concerning this invention can be tablet-ized to the thing of a pharmaceutical form well-known as an external application tablet. As a pharmaceutical form of this tablet, a pasting agent, a patch agent, a tape, ointment, gel, cream pharmaceuticals, liquid medicine, etc. are mentioned.

[0012] Especially as an external application basis added by the medicine for external application concerning this invention, it is not restricted but the water soluble polymer usually used, a surfactant, a stabilizing agent, pH regulator, etc. can be mentioned. As a water soluble polymer, all of a polyacrylic acid, sodium polyacrylate, a carboxyvinyl polymer, KARUME sirloin sodium, polyvinyl alcohol, a polyvinyl pyrrolidone, hydroxypropylcellulose, a hydroxyethyl cellulose, an ethyl cellulose, an alginic acid, a sodium alginate, gelatin, and a methyl vinyl ether, a maleic-anhydride copolymer, etc. are usable, for example.

[0013] As a surfactant, polyoxyethylene sorbitan fatty acid ester, a sorbitan fatty acid ester, polyoxyethylene alkyl phenyl ether, etc. can be mentioned, for example. As a stabilizing agent, a sodium hydrogensulfite, L ascorbic acid, a sodium ascorbate, burylhydroxyanisole, butylhydroxytoluene, a propyl gallate, tocopherol acetate, an dl-alpha-tocopherol, a sodium hydrogensulfite, etc. are mentioned, for example.

[0014] As a pH regulator, a diisopropanolamine, a diethanolamine, a triethanolamine, a citric acid, a tartaric acid, etc. are mentioned, for example. As a pharmaceutical form of the medicine for external application concerning this invention, since the absorptivity (durability) of a medicine, safety, and use are simple, a pasting agent is the most desirable pharmaceutical form. A cross linking agent, a bulking agent, etc. which are usually used besides each above-mentioned basis are suitably used for this pasting agent.

[0015] As a cross linking agent, aluminium compounds, such as inorganic or the salt of an organic acid like an aluminum hydroxide and an aluminum stearate, double salt like aluminum alum, inorganic nature aluminum complex salt, and an organic nature aluminum chelate compound, are mentioned, for example. Moreover, as a bulking agent, a kaolin, titanium oxide, a zinc oxide, a silicic acid anhydride, etc. are mentioned, for example. In addition to this, a thickener, a tackifier, antiseptics, an aromatizing agent, a coloring agent, etc. can be suitably blended with the medicine for external application of this invention if needed.

[0016] Although an example explains this invention concretely below, this invention is not limited to the following example, unless the main point is changed.

[0017] An example 1 and an example 2 (pasting agent)

処方	実施例1	実施例2
(1) 水溶性高分子	8.0	8.0
(2) 架橋剤	0.31	0.31
(3) 充填剤	0.25	0.25
(4) ﾒﾁﾙﾊﾟﾗﾍﾞﾝ	0.1	0.1
(5) ﾌﾟﾛﾋﾟﾙﾊﾟﾗﾍﾞﾝ	0.05	0.05
(6) ｸﾞﾘｾﾘﾝ	25.0	25.0
(7) ﾍﾟﾝｼﾞﾙｱﾙｺｰﾙ	5.0	5.0
(8) 界面活性剤	1.0	1.0
(9) ﾒｼﾙ酸ﾌﾟﾛﾋﾟﾚﾝｸﾞﾘｺｰﾙ	0.5	1.0
(10) ｴﾃﾞﾄ酸ﾅﾄﾘｳﾑ	0.25	0.25
(11) pH調整剤	0.6	0.6
(12) 精製水	57.94	57.44
合 計	100.0%	100.0%

[Table 1] Table 1

[0018] (A) (1) An agitator may be used and - (6) is mixed, and (7) which melted (8) further is added and it often mixes.
(B) (9) - (11) is dissolved in (12).
(C) Add (B) to (A) and carry out churning mixture uniformly.

(D) Spread this plaster body to a nonwoven fabric, cover with polyester film, and obtain a pasting agent.

[0019] Example 3 (gel)

(処方)

(1)	メシル酸プリジノール	1%
(2)	グリセリン	10%
(3)	ベンジルアルコール	5%
(4)	水溶性高分子	2%
(5)	pH調整剤	適量
(6)	精製水	適量
	合計	100%

(A) Make (6) swell (4).

(B) Dissolve (1) in (2) and (3).

(C) Agitate until it adds (A) and (5) to (B) and the whole becomes uniform, and consider as gel.

[0020] Example 4 (liquid medicine)

(処方)

(1)	メシル酸プリジノール	1%
(2)	ベンジルアルコール	5%
(3)	グリセリン	20%
(4)	pH調整剤	適量
(5)	精製水	適量
	合計	100%

(A) (1) Dissolution mixture of - (5) is carried out uniformly, and it considers as liquid medicine.

[0021] The example 1 of comparison, and the example 2 (pasting agent) of comparison

[Table 2] Table 2

処　方	比較例1	比較例2
(1) 精製水	55.95	55.45
(2) 酒石酸	0.9	0.9
(3) ﾒｼﾙ酸ﾌﾟﾘｼﾞﾉｰﾙ	0.5	1
(4) ｸﾞﾘｾﾘﾝ	30	30
(5) 軽質無水ｹｲ酸	2	2
(6) 水溶性高分子	7	7
(7) 架橋剤	0.2	0.2
(8) 界面活性剤	0.6	0.6
(9) ﾊｯｶ油	1	1
(10) ｼﾞｲｿﾌﾟﾛﾊﾟﾉｰﾙｱﾐﾝ	適量	適量
合　計	100.0%	100.0%

[0022] (A) Add (2) and (3) to (1) and dissolve in it.

(B) Add (4) - (10) to (A) and mix with it uniformly.

(C) Spread this plaster body to a nonwoven fabric, cover with polyester film, and obtain a pasting agent.

[0023] The example 3 (gel) of comparison

(処方)

(1)	メシル酸プリジノール	1%
(2)	ベンジルアルコール	5%
(3)	水溶性高分子	2%
(4)	pH調整剤	適量
(5)	精製水	適量
	合計	100%

(A) Make (5) swell (3).

(B) Dissolve (1) in (2).

(C) Agitate until it adds (A) and (4) to (B) and the whole becomes uniform, and consider as gel.

[0024] The example 4 (gel) of comparison

(処方)

(1)	メシル酸プリジノール	1%
(2)	グリセリン	10%
(3)	水溶性高分子	2%
(4)	pH調整剤	適量
(5)	精製水	適量
	合計	100%

(A) Make (5) swell (3).

(B) Dissolve (1) in (2).

(C) Agitate until it adds (A) and (4) to (B) and the whole becomes uniform.
[0025] The example 5 (liquid medicine) of comparison

(処方)

(1)	メシル酸プリジノール	1％
(2)	ベンジルアルコール	5％
(3)	プロピレングリコール	20％
(4)	pH調整剤	適量
(5)	精製水	適量
	合計	100％

(A) (1) Dissolution mixture of - (5) is carried out uniformly.
[0026] The example 6 (liquid medicine) of comparison

(処方)

(1)	メシル酸プリジノール	1％
(2)	ベンジルアルコール	5％
(3)	1，3－ブチレングリコール	20％
(4)	pH調整剤	適量
(5)	精製水	適量
	合計	100％

(A) (1) Dissolution mixture of - (5) is carried out uniformly.
[0027] The example [of an examination] 1 experiment method: The pasting agent prepared by the method indicated for the example 2, the example 1 of comparison, and the example 2 of comparison was sealed with the aluminum lamination wrapping material, and after saving for two weeks in a 60-degree C thermostat, the appearance change on the front face of a plaster body was observed. The result is shown in Table 3.
Result: Although the deposit of the crystal of mesyl acid PURIJI Norian was accepted in all about the pasting agent of the example 1 of comparison, and the example 2 of comparison, in the pasting agent of the example 2 in this invention, the deposit of a crystal was not seen at all.
[0028]

[Table 3] Table 3

処 方	外 観
実施例2	変化なし
比較例1	メシル酸プリジノールの結晶が析出
比較例2	メシル酸プリジノールの結晶が析出

[0029] The comparison examination of skin permeability was carried out to example of examination 2 example 1, the example 2, the example 1 of comparison, and the example 2 of comparison by the following experiment method about each pasting agent prepared by the method of a publication. The result is shown in drawing 1 .
The experiment method: It carried out depilating of the back hair of 7 weeks old and a femaleness hair loess rat (135g of average weight) by electric hair clipper on the experiment previous day. The back skin was extracted after carrying out cervical-vertebra dislocation of the hair loess rat which carried out depilating on the previous day. The extraction skin was fixed to the Francis type diffusion cell (diameter of 2cm), the pasting agent (they are about 1.3mg (an example 1, example 1 of comparison) and about 2.7mg (an example 2, example 2 of comparison) as mesyl acid PURIJI Norian) of examples 1 and 2 and the examples 1 and 2 of comparison was stuck on the donor side, respectively, and the physiological saline was filled to the receptor side. During the experiment, the receptor side maintained 37 degrees C and agitated them with the magnetic stirrer. The constant rate was extracted from the receptor side for every predetermined time, and the amount of transparency of mesyl acid PURIJI Norian was measured using the high performance chromatography.
[0030] Result: As compared with the thing of each example of comparison, penetrable elevation was seen with elevation of medicine concentration, and, as for this invention article, high percutaneous absorption was accepted so that clearly from drawing 1 . Since it compared with this and saturated concentration was already reached with 0.5% (example 1 of comparison) of medicine concentration in the example of comparison, the penetrable elevation beyond this was not seen as for 1.0% (example 2 of comparison) of medicine concentration, but percutaneous absorption was low as compared with this invention article.
[0031] The absorption moving state was measured about each pasting agent prepared by the method of a publication for the example of examination 3. example 2, and the example 2 of comparison.
The experiment method: It carried out depilating of the regions-of-back hair of 8 weeks old and a femaleness hair loess rat (136.5g of average weight) by electric hair clipper on the experiment previous day, and abstained from food further. the pasting agent (4x2.5cm) of an example 2 and the example 2 of comparison -- the median line was avoided on the rat regions-of-back skin which carried out depilating of the one sheet (about 7mg as mesyl acid PURIJI Norian) on the previous day, it stuck on right-hand side, and a it top was fixed by the adhesive tape for fixation, and the surge cull tape (3M) was stuck and it fixed so that the truncus section might be wrapped in further It collected blood in 4ml of blood from the abdomen inferior vena cava under anesthesia after (medication 4 and 8 and 16 hours). After having taken 0.75ml of blood serums after

centrifugal separation (3000rpm, 20 minutes), making blood alkaline by the sodium hydroxide and extracting mesyl acid PURIJI Norian using the petroleum ether, the concentration in a blood serum was measured using the high performance chromatography.

[0032] Result: Each measured value which shows the pharmacokinetics is shown in Table 4. The pasting agent of this invention maintained the mesyl acid PURIJI Norian concentration in blood stabilized until after 16 hours, and Cmax and AUC have exceeded it under the influence of an absorption accelerator as compared with the example 2 of comparison, and high percutaneous absorption was accepted.

[0033]

[Table 4] Table 4

製剤	投与量	血中濃度 (ng/ml) 4hr	8hr	16hr	Tmax (hr)	Cmax (ng/ml)	AUC (ng·hr/ml)
実施例2	7mg/ラット	89.4	110.2	60.1	8	110.2	1258.8
比較例2	7mg/ラット	56.8	84.9	51.4	8	84.9	742.9

(Note) Tmax : The highest blood-drug-concentration attainment time Cmax : The highest blood drug concentration AUC : Blood-drug-concentration time curvilinear inferior-surface-of-tongue product [0034] The comparison examination of skin permeability was carried out to the example 2 of an examination by the method of a publication about each gel prepared by the method indicated for the example of examination 4. example 3, the example 3 of comparison, and the example 4 of comparison. Moreover, observation of appearance and comparison of a feeling of inunction were performed simultaneously. The result of a skin permeability examination is shown in drawing 2 .

Result: Although it is inferior to percutaneous absorption and the facilitatory effect was seen [the glycerol of the example 4 of comparison] also by the benzyl alcohol independent of the example 3 of comparison so that clearly from drawing 2 , it was admitted that this invention article blended combining both maintained high percutaneous absorption. moreover, the thing for which this invention article (example 3) blends a glycerol although benzyl alcohol looms in the example 3 of comparison, ** is seen observation of appearance, and as a result of comparison of a feeling of an application and a feeling of inunction is bad -- the dispersibility of benzyl alcohol -- good -- becoming -- moreover, benzyl alcohol -- also coming up -- it did not accept but the improvement of a feeling of inunction was accepted

[0035] The comparison examination of skin permeability was carried out to the example of examination 5. example 4, the example 5 of comparison, and the example 6 of comparison by the method of a publication about each solution prepared by the method of a publication at the example 2 of an examination. The result is shown in drawing 3 .

Result: As compared with the solution by combination with the propylene glycol which was shown in the example of comparison and which is said for there to be a percutaneous absorption promotion operation generally, or 1 and 3-butylene glycol, very high percutaneous absorption was accepted in the solution blended combining the benzyl alcohol and the glycerol of this invention article so that clearly from drawing 3 .

[Translation done.]

DESCRIPTION OF DRAWINGS

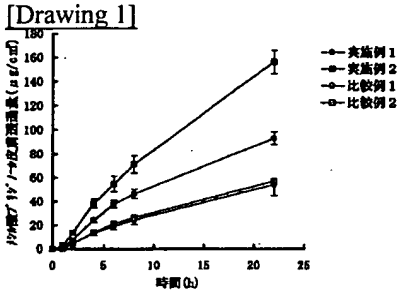
[Brief Description of the Drawings]
[Drawing 1] It is the graph which shows transition of the amount of skin transparency of the examples 1 and 2 and the examples 1 and 2 of comparison concerning this invention.
[Drawing 2] It is the graph which shows the amount of skin transparency 22 hours after the example 3 and the examples 3 and 4 of comparison concerning this invention.
[Drawing 3] It is the graph which shows the amount of skin transparency 22 hours after the example 4 and the examples 5 and 6 of comparison concerning this invention.

[Translation done.]

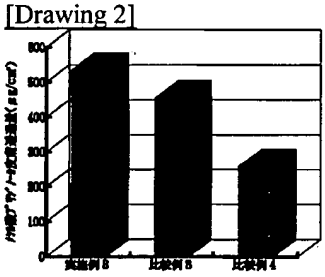
[Translation done.]

DRAWINGS

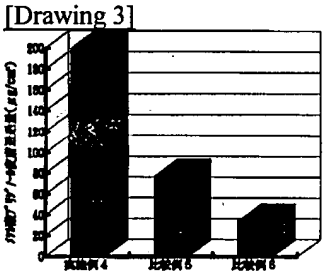
[Drawing 1]



[Drawing 2]



[Drawing 3]



[Translation done.]

* NOTICES *

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1. This document has been translated by computer.So the translation may not reflect the original precisely.
2. **** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CORRECTION or AMENDMENT

[Official Gazette Type] Printing of amendment by the convention of 2 of Article 17 of patent law.
[Section partition] The 2nd partition of the 3rd section.
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A61K 31/445 AAS
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363
47/10 G
E

[Procedure revision]
[Filing Date] May 24, Heisei 14 (2002. 5.24)
[Procedure amendment 1]
[Document to be Amended] Specification.
[Item(s) to be Amended] Claim.
[Method of Amendment] Change.
[Proposed Amendment]
[Claim(s)]
[Claim 1] The mesyl acid PURIJI Norian content medicine for external application which does not contain a polyfunctional epoxy compound as a cross linking agent including mesyl acid PURIJI Norian, a glycerol, benzyl alcohol, and an external application basis.
[Claim 2] The medicine for external application according to claim 1 whose benzyl alcohol a glycerol is 5 - 30 % of the weight, and is 1 - 20 % of the weight.
[Claim 3] The medicine for external application according to claim 1 whose benzyl alcohol a glycerol is 10 - 25 % of the weight, and is 5 - 10 % of the weight.
[Claim 4] The medicine for external application according to claim 1 to 3 whose dosage forms of a medicine for external application are the things of a pasting agent.
[Procedure amendment 2]
[Document to be Amended] Specification.

[Item(s) to be Amended] 0005.
[Method of Amendment] Change.
[Proposed Amendment]
[0005]
[Description of the Invention] This invention persons succeeded in development of the mesyl acid PURIJI Norian content medicine for external application which was excellent in percutaneous absorption and durability, and was excellent in a feeling of use by making a glycerol and benzyl alcohol blend with mesyl acid PURIJI Norian, as a result of repeating research wholeheartedly in such a situation. That is, the mesyl acid PURIJI Norian content medicine for external application characterized by this invention not containing a polyfunctional epoxy compound as a cross linking agent including mesyl acid PURIJI Norian, a glycerol, benzyl alcohol, and an external application basis is offered, and this invention offers further the mesyl acid PURIJI Norian content medicine for external application which is the thing of a pasting agent as a thing of the desirable dosage forms of this medicine for external application.
[Procedure amendment 3]
[Document to be Amended] Specification.
[Item(s) to be Amended] 0008.
[Method of Amendment] Change.
[Proposed Amendment]
[0008] The blending ratio of coal of the glycerol in the medicine for external application concerning this invention is preferably blended at 10 - 25% still more preferably 5 to 30% one to 50% of the weight (in this specification, it only displays by % hereafter). If there are many loadings of a glycerol, the inclination for the percutaneous absorption of mesyl acid PURIJI Norian to fall will be seen. On the other hand, if there are few loadings, the problem that the dispersibility of a fine-particles component is bad and lacks in workability and homogeneity on the occasion of tablet-izing will arise. Moreover, since plasticity becomes [dosage forms] bad about the thing of a pasting agent, the good pasting agent of a feeling of use is not obtained. Moreover, a glycerol is matter which has the advantage that it is low stimulative as compared with other glycols.
[Procedure amendment 4]
[Document to be Amended] Specification.
[Item(s) to be Amended] 0011.
[Method of Amendment] Change.
[Proposed Amendment]
[0011] Generally the medicine for external application concerning this invention can be tablet-ized to the thing of dosage [Section partition] The 2nd partition of the 3rd section. □nslation may not reflect the original precisely. □ a patch agent, a tape, ointment, gel, cream pharmaceuticals, liquid medicine, etc. are mentioned.
[Procedure amendment 5]
[Document to be Amended] Specification.
[Item(s) to be Amended] 0014.
[Method of Amendment] Change.
[Proposed Amendment]
[0014] As a pH regulator, a diisopropanolamine, a diethanolamine, a triethanolamine, a citric acid, a tartaric acid, etc. are mentioned, for example. As dosage forms of the medicine for external application concerning this invention, since the absorptivity (durability) of a medicine, safety, and use are simple, pasting agents are the most desirable dosage forms. A cross linking agent, a bulking agent, etc. which are usually used besides each above-mentioned basis are suitably used for this pasting agent.

[Translation done.]